REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 30-58 and 64 are in this case. Claims 30-58 and 64 have been rejected. Claims 30-58 and 64 have now been cancelled. New claims 65-74 have now been added.

Information Disclosure Statement

The Examiner states that the IDS filed December 4, 2002 fails in part to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because several publications cited therein lack publication dates, title, author and/or relevant pages. A supplemental IDS which corrects these errors is enclosed herewith.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 30-58 and 64 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 30-58 and 64 have now been cancelled. New claims 65-74 have now been added.

In the interest of expediting prosecution in this case, new independent claims 65, and 70 now recite "at least 2 and no more than 20 naturally occurring monosaccharide units" thus clearly defining the nature and size of the complex carbohydrate structures of the library synthesized according to the teachings of the present invention. Support for these claim amendments can be found throughout the instant application. For example, size limitations can be found Example 6 of the instant application, while description of the type of monosaccharides utilized for library synthesis can be found on page 44, lines 20-24. New claims 65-74 also forgo the use of the language which was the basis for the new matter rejections presented by the Examiner.

In view of the above arguments and claim amendments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 30-58 and 64 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claim 30-58 and 64 have now been cancelled. New claims 65-74 have now been added.

The Examiner points out that the phrase "complex carbohydrate" is relative and undefined and that claims 30-58 are incomplete for omitting an essential synthesis step.

As is argued with respect to the 112, first paragraph, rejections, new independent claims 65 and 70 now recite limitations which clearly define the size of the complex carbohydrates of the library. In addition, these claims now include a synthesis step.

In view of these claim amendments, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 102(b) Rejections - Fodor et al.

The Examiner has rejected claims 30-58 and 64 under 35 U.S.C. § 102(b) as being anticipated by Fodor et al. (U.S. Pat. No. 5,424,186). The Examiner's rejections are respectfully traversed. Claims 30-58 and 64 have now been cancelled. New claims 65-74 have now been added.

The Examiner states that Fodor et al. describe the production of complex polysaccharides on an addressable VLSIPS using enzymatic synthesis.

New claims 65-74 now include several limitations which in the opinion of the Applicant clearly distinct the present invention from Fodor et al.

Applicant would like to point out that although Fodor et al. mention the application of enzymes in carbohydrate synthesis, the teachings of U.S. Pat. No. 5,424,186 clearly focus on photo-activatable chemical synthesis and as such, no clear description or suggestion of synthesis of branched polysaccharides using enzymatic approaches is set forth in this document. Rather, Fodor et al. concentrate on outlining a chemical synthesis approach which is highly suitable for the parallel synthesis of linear polymers such as polypeptides and polynucleotides, and can also be applied towards the synthesis of linear polysaccharides.

As is well known in the art, enzymatic synthesis of polymers has several advantages over the widely utilized chemical synthesis approaches.

One important advantage, especially when constructing polymer arrays is the ability to carefully control the synthesis reaction and synthesize a polymer of a predetermined structure and stereo-specificity. Although elaborate, carefully planned chemical synthesis reactions can be utilized to accurately synthesize the structure of several relatively simple macromolecules, such reactions cannot be effectively utilized to generate structures of known stereo-specificity, since such reactions typically result in a combination of alpha and beta anomers (see the first Figure of Appendix 2).

Uniform stereo-specificity is vital when such carbohydrates are utilized for screening, since binding of biomolecules or drug candidates to such carbohydrates can be affected by such features.

Since enzymatic reactions are stereo-specific, a resultant carbohydrate population synthesized using such an approach would include a single anomer as opposed to the racemic mixture of carbohydrates that would result from chemical synthesis, even one which utilizes the photo protective groups described by Fodor et al.

Defined stereo-specificity can only be attributed to a carbohydrate library which was fully synthesized using carefully planned enzymatic synthesis steps and thus the methods and resulting product of the present invention are clearly distinct from the prior art cited by the Examiner. Description of this feature can be found throughout the instant application (see, for example, page 11, line 8) although it will be appreciated that such description is not necessary since, as is well known in the art, stereo-specificity is inherent to enzymatic synthesis.

In addition, enzymatic synthesis also ensures that synthesis of branched carbohydrates results in a uniform carbohydrate population of a single branched structure and not, as is the case with chemical synthesis, a mixed carbohydrate population which includes several different branched structures.

The differences between the synthesis products generated using the present approach and that described by Fodor et al. are outlined in the enclosed Appendix 2 which illustrates the synthesis of a branched polysaccharide. As is shown in the Appendix, using the approach described by Fodor et al. leads to the generation of a mixture of polysaccharides each having a different branch point and thus a totally

different structure and possibly characteristics, whereas applying the approach of the present invention results in a carbohydrate population of a single structure.

Thus, only the present approach enables synthesis of branched carbohydrate populations with specific and uniform branching patterns. Support for synthesis of branched carbohydrates can be found throughout the instant application.

It will be appreciated that although Fodor et al. mentions branched synthesis on column 16 lines 22-26 this text does not, in any way, describe enzymatic synthesis of branches but rather outlines photo activatable chemical synthesis of branches (i.e., by using a protecting group at different locations), an approach which, as is illustrated in the enclosed appendix, cannot be utilized to generate a population of complex carbohydrates of a single branched structure.

Applicant would like to point out that although it would appear from the text of column 17, lines 50-62 that Fodor et al. describe branched synthesis, careful review of this text reveals that Fodor et al. does not teach synthesis of predetermined branched structures (i.e. of known branching patterns) but is merely suggesting a novel approach which can be used for parallel synthesis of polymers using several photo labile groups rather than masks. Although Fodor et al. suggest that this approach can also be used for branched synthesis (column 17 line 58) this suggestion is not elaborated upon and thus Applicant strongly believes that it does not represent disclosure which can be considered as prior art in this case. Although Applicant fully understands that the enablement and written description requirements are far less stringent when considering prior art as opposed to an examined application, Applicant contends that Fodor et al. does not provide any enablement or written description for a method of generating branched structures using several types of protecting groups. In addition, due to the diffuse unfocused nature of the teachings provided by the text of column 17, it is Applicant's strong opinion that this text would not motivate one of ordinary skill in the art to utilize photo labile protecting groups for directed synthesis of predetermined branched structures, since using such an approach would require the artisan to conduct time consuming experimentation in order to formulate an approach which can be effectively used to generate branched carbohydrates of a predetermined structure.

In addition, it should also be noted that although combining chemical synthesis with enzymatic reactions is theoretically possible, in the case of Fodor et al. such

combination would not since the monosaccharides building blocks utilized by the method described by Fodor et al are modified (i.e. include a protective group) and as was noted by the Examiner with respect to this application, enzymatic reactions which target such modified saccharides would not be efficient and accurate.

Notwithstanding from the above, Applicant has also elected to introduce limitations which pertain to the linker utilized to attach the carbohydrate structures to the array. Such limitations find support on page 83, line 9 to page 84 line 11, and on page 87 lines 9-14 of the instant application. Additional support can also be found in Figures 5a-b of the instant application. The advantages of using such a linker in subsequent library use are outlined in the appendix attached herewith. As is described therein, the specific linker composition of claim 70 presents numerous advantages in particular when utilizing the array-bound library of the present invention for the purpose of screening antibodies. Further description of the advantages of using such a linker and data pertaining to experiments conducted with such a linker are provided in the Appendix 1 enclosed herewith. The experiments described therein compare an ability of carbohydrate binding proteins to bind various complex carbohydrate structures which are attached to an array via various types of linkers. The results clearly demonstrate that both the chemical nature of the linker and its length dramatically affect non-specific as well as specific binding between these proteins and the complex carbohydrates of the array and illustrate that the linker composition described in claim 70 enabled the best binding performance.

35 U.S.C. § 103(a) Rejections - Fodor et al. in view of Seitz et al. and Seifert et al.

The Examiner has rejected claims 30-58 and 64 under 35 U.S.C. § 103(a) as being unpatentable over Fodor et al. in view of Seitz et al. The Examiner's rejections are respectfully traversed. Claims 30-58 and 64 have now been cancelled. New claims 65-74 have now been added.

Arguments with respect to Fodor et al. are presented above. Since it is the opinion of the Applicant that the present invention as now claimed is not anticipated or rendered obvious by the teachings of Fodor et al., and since Seitz et al. and Seifert et al. do not describe or suggest the use of the linker of claim 70, or enzymatic approaches which are suitable for on-chip parallel synthesis of addressable carbohydrates and in

particular branched carbohydrates, it is respectfully submitted that the combined teachings of these prior art documents would not motivate the ordinary skilled artisan to make the present invention.

35 U.S.C. § 103(a) Rejections

Dower et al. in view of Nicolaou et al. and Schuster et al.

The Examiner has rejected claims 30-34, 36-40, 44-51 and 53-58 under 35 U.S.C. § 103(a) as being unpatentable over Dower et al. in view of Nicolaou et al. and further in view of Schuster et al. The Examiner's rejections are respectfully traversed. Claims 1, 3-5, 8, 10, 16-27 and 29 have now been cancelled. New claims 65-74 have now been added.

The present invention is of a method of synthesizing a complex carbohydrate library in which each member of the library is bound at a specific and addressable location of an array. Although Applicant believes that these qualities clearly distinct the present invention from the prior art cited by the Examiner, it will be appreciated that the limitations presented in new claims 65-74 and the arguments presented above with respect to the Fodor et al. rejection further distinct the present invention as claimed from the teachings of Dower et al., Nicolaou et al. and Schuster et al.

Since the instant application was the first to describe in detail the enzymatic synthesis of branched complex carbohydrates which are identifiable via their location on the array, and since such arrays are neither described nor are they suggested by Dower et al., Nicolaou et al. or Schuster et al., these prior art documents, alone or in combination, clearly would not motivate the ordinary skilled artisan to make the present invention.

In view of the above amendments and remarks it is respectfully submitted that New claims 65-74 ar now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: September 29, 2003

Encl.:
3-months extension fees
supplemental IDS
Appendices 1-2

Appendix 1

Effect of the chemical nature and length f linker on signal intensity

The following set of experiments were done to compare between the performance of two types of linker (Linker 1 and linker 2 in Figure 1) with respect to specific and non specific binding to glycans attached thereto. The length of the linkers is controlled by the number of elongation cycles (see Figure 4). For the synthesis of linker type 2 we have use 1,8 - diaminooctane instead of 1,8-diamino 3,6 dioxaoctane As a model we have tested the binding of biotinlated lectin BS-I from *Bandeiraea simplicifolia* which have binding specificity to Galactose α, and the lectin WGA from wheat germ that have binding specificity to GlcNac . The detection of lectin binding to Galactose on the surface was done by secondary labeling of bound lectin with florescent labeled streptavidin.

Figure 2 described the signal to background ratio that were measured for each linker type at different length For BS-I. The back ground was measured in wells containing linker (either type 1 or 2) attached to p-Nitrophenol instead of p-Nitrophenyl α Galactose, thus having terminal OH group. Figure 3 A and B describe the absolute signal for each linker type. Figure 5 described the signal to background ratio that were measured for each linker type at different length for WGA. It is clear the linker 1 have superior performance in respect to both specific and non specific binding of proteins. It has low non specific binding and it enable high specific binding of lectins to the carbohydrate ligand attached thereto.